

Appl. No. 09/891,138
Amdt. dated August 11, 2004
Amendment under 37 CFR 1.116 Expedited Procedure

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REMARKS

With entry of the instant amendment, claims 1, 2, 5, 15, and 18 are newly cancelled. Claims 4, 8-12, 14, 16, 17, 19-29, and 32-67 were previously cancelled. Accordingly, claims 3, 6, 7, 13, 15, 30, and 31 are pending in the application.

Claims 3, 13, and 30 are amended. The amendments add no new matter.

The Examiner's comments will be addressed in the order presented in the Office Action mailed February 20, 2004.

Applicants thank the Examiner and Primary Examiner for the interview on June 22, 2004, a summary of which was mailed by the Examiner on June 22, 2004. The summary indicated that Applicants need not submit an additional summary.

Rejection under 35 U.S.C. § 101

The rejection alleging that the claimed nucleic acid sequences lack a specific and substantial utility was maintained. The Examiner argues that the Declaration under 37 C.F.R. § 1.132 by Daniel Lin filed with Applicants' previous response is insufficient in establishing anything specific about the receptor. Although the Examiner acknowledges that the data in the Declaration shows that the claimed GPCR is an active receptor (page 3, last sentence of the Office Action), he contends that nothing specific about the receptor, such as its tissue or origin, is presented. The Examiner also argues that the asserted utility is not substantial, as further research is required to determine how to use the claimed receptor. Applicants respectfully traverse.

First, Applicants note that the specification discloses on page 7, lines 7-9 that mouse TGR18 is abundantly expressed in the kidney. The specification also teaches that mouse TGR18 is an active GPCR (*e.g.*, page 10, lines 11-19). Further, Applicants teach that TGR18 can participate in the modulation of cellular function in cells, for example kidney cells, in which it is expressed (*e.g.*, page 51, lines 31-34); and that a GPCR that is predominantly expressed in the kidney can play a role in renal disease, *e.g.*, hypertension (page 52, lines 2-6). The specification discloses that such a GPCR has various uses, *e.g.*, it can be used to modulate kidney

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cell function (*see, e.g.*, page 7, lines 7-8 and 12-14). The Examiner acknowledges that the asserted utilities are credible; Applicants further submit that the asserted utilities are specific and substantial under the guidelines set forth in the MPEP at § 2107.01(I). For example, the utilities are specific in that they relate to a biological function of a GPCR in the kidney; they are substantial in that they relate to real world use. Although Applicants believe that the Rule 1.132 Declaration by Daniel Lin filed October 15, 2003 providing data showing that mouse TGR18 has GPCR activity is sufficient to address the utility rejection, in order to expedite prosecution, submitted herewith is further evidence in support of the asserted utilities.

The publication (He, *et. al.*, *Nature*, 429:188-193, 2004), attached as Appendix A, describes that mouse GPR91 (which corresponds to TGR18; *see*, the Rule 1.132 Declaration by Daniel Lin accompanying this response) has GPCR activity. He, *et al.* also teach that the role of succinate as a ligand for a GPCR was an unexpected finding (*see, e.g.*, the abstract, page 188, column 1). Accordingly, succinate does not appear to be regarded by those in the art as a general stimulator of GPCR activity.

He, *et al.* also describes earlier work that provides a biologically relevant context for succinate and consequently, TGR18, in the kidney. For example, succinate was known to increase the reabsorption of phosphate and glucose into the proximal tubule (*see*, page 192, the first full paragraph of column 1). Further, succinate-treated kidney culture *ex vivo* release renin (page 191, first column, last paragraph). These effects were known prior to the filing date of the application, as evidenced by the publication dates of the references cited at the indicated passages.

Moreover, the paper provides data showing that succinate induces hypertension in normal mice. In GPR91-deficient animals, however, succinate did not induce hypertension (*see, e.g.*, page 191, second column, last paragraph). Thus, He, *et al.* provide additional data demonstrating the biological relevance of TGR18 in the kidney, as taught in the instant application. In view of the biological role of TGR18, TGR18 nucleic acid and polypeptides sequences have credible, substantial, and specific uses. Applicants therefore respectfully request

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withdrawal of the utility rejection and the associated rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, first paragraph--enablement

The claims were also rejected as allegedly not enabled. The Examiner contends that it would require undue experimentation to identify fragments, derivatives, muteins, and sequence variants of SEQ ID NO:1. To the extent that the rejection applies to the amended claims, Applicants respectfully traverse.

The Examiner first argues that it would be physically impossible to have a GPCR with only 25 amino acids, 100 amino acids or 200 amino acids. Although the claims reciting these elements have been cancelled, thereby rendering this aspect of the rejection moot, Applicants note that the specification teaches chimeric molecules (*see, e.g.*, page 40, lines 11-25) in which domains or other regions of the claimed sequences are used in the context of a heterologous protein that have activity. Thus, it is in fact possible to have a polypeptide that has GPCR activity and comprises only 25 amino acids, 100 amino acids, or 200 amino acids of the claimed sequence.

The Examiner also contends that Applicants do not provide adequate guidance in the specification to reasonably predict the positions in the mouse TGR18 sequence that can be successfully substituted. Applicants disagree. First, as the Examiner acknowledges in section 35 of the Office Action, much is known about the structure of GPCR domains. Sequence alignment algorithms are well known in the art (*see, e.g.*, the direction provided in the passage starting at page 18, line 32). The Examiner provides no evidence or reasoning as to why one of skill could not reasonably determine residues to be substituted or mutated such that an active sequence that is almost identical, *i.e.*, is at least 95% identical, could be generated based on a comparison between the mouse and other known GPCR sequence. Indeed, He *et al.*, *supra*, also show that human and rat GPR91 are active, thus providing additional evidence that variant TGR91 sequences having GPCR activity can be generated. Accordingly, the Examiner's argument fails to establish that undue experimentation is required.

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Please note with regard to the Examiner's comment in section 27 of the Office Action, Applicants response to the previous Office Action filed October 15, 2003 cites to MPEP § 2164.08 twice. The second citation of that section on page 10 of Applicants' response inadvertently had a typographical error. The proper passage is MPEP § 2164.08, not § 2168.08.

Rejections under 35 U.S.C. § 112, first paragraph written description

The Examiner alleges that claims 1-3, 5-7, 13, 15, 18, 30, and 31 lack adequate written description support. Applicants traverse for reasons of record. The additional arguments presented by the Examiner are addressed below.

The Examiner appears to be arguing in section 32 that percent identity, as cited in the present claims, is an insufficient structural parameter with no functional value, particularly in view of the alleged lack of utility of the reference sequence. He further contends that the fact pattern in the instant application does not correspond to Example 14, which recites percent identity, of the "Revised Interim Written Description Guidelines", Federal Register, Vol. 66, No. 4, 1099, January 5, 2001, because the enzymes in Example 14 are not analogous to GPCR polypeptides (section 33 of the Office Action). As noted above, Applicants disagree.

First, the claimed sequences have utility, as explained above. Furthermore, it is not clear from the argument presented in the Office Action why the Examiner believes that percent identity to a reference sequence does not represent a structural recitation. Example 14 does in fact indicate that percent identity terms provides a feature. Applicants submit that the GPCR sequences of the instant application, like the sequence in Example 14, do not exist in a context devoid of the knowledge of similar sequences. GPCRs generally have conserved structural features, as noted by the Examiner in paragraph 35 of the Office Action, and as taught in the specification on page 10. Further, exemplary conservative substitutions are described in the section beginning on page 15. Last, related sequences, e.g., the human sequence disclosed in U.S. Patent 5,871,963, are known. The Examiner fails to explain why general knowledge of GPCR structure and knowledge of the structure of a related sequence in combination with the

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teachings in the specification does not constitute proper written description for nucleic acids encoding sequences having at least 95% identity to the reference sequence.

With regard to the points raised in sections 34 and 35 of the Office Action, these are moot in view of the cancellation of the claims reciting the terms referred to in the two sections.

In view of the foregoing, Applicants believe that all of the claims are adequately supported by proper description. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Jean M. Lockyer
Reg. No. 44,879

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
JML:jml
60243294 v1